Clinical Pharmacology and Biopharmaceutics Review

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Consultant Reviewer:	Raymond Miller, D.Sc.

Population Pharmacokinetic Analysis

Protocol No.: 16.0016

Study Title: Safety, Population Pharmacokinetics, and Efficacy of Recombinant Human Tumor Necrosis Factor Receptor Fc Fusion Protein (TNFR:Fc) in Children with Juvenile Rheumatoid Arthritis.

Study Site: Multicenter

Investigators: G.D. Cawkwell, A. Gedalia, N.T. Ilowite, D.J. Lovell, J.C. Olson, A. Reiff, E.D. Silverman, L.D. Stein, C.A. Wallace.

Objective: The objectives of part I of the study, were to determine the safety and population pharmacokinetics of (TNFR:Fc) in pediatric patients with active polyarticular course juvenile rheumatoid arthritis (JRA) and patient response to TNFR:Fc at day 90. This report deals only with the population pharmacokinetic analysis of TNFR:Fc in these patients.

Methods: Nonlinear mixed effect modeling was used to fit the model to the data. Goodness of fit criteria were likelihood ratio test and graphical analysis of residual plots.

Study Design: Patients received 0.4 mg/kg (maximum 25 mg) twice weekly for 90 days. Serum samples for population PK were drawn on Days 1 (before administration of study drug) and 15; at the end of months 1, 2, and 3; and 30 days after discontinuation of study drug (or at the end of Month 4 for patients continuing into part 2 of the study). Samples in this study were drawn at random times relative to administration of study medication. A population pharmacokinetic analysis was performed using all of the TNFR:Fc concentrations in serum samples collected throughout clinical development in addition to the serum samples collected in this study. Model development was done using data from Studies 16.9125, 16.9203, 16.0001, 16.0002, 16.0004, 16.0006, 16.0008, 16.0010, 16.0014, 16.0016, 16.0017. The analysis was done with 370 blood samples from 69 pediatric patients among the total of approximately 2980 samples from 332 patients and healthy volunteers in the clinical development program.

The model was developed adding explanatory covariates and a final model was selected by model reduction.

Reviewer Comment: The combination of all the previously obtained blood levels with the current blood level data is a good way of using rich data sets (prior study) with sparse data sets (current study) to determine pharmacokinetic parameters in special population groups, in this case pediatric patients. The rich data provides information to determine the structural model i.e. two compartment model, lag time, bioavailability, while the sparse data provides reasonable estimates of pharmacokinetic parameters as well

as the influence of covariates such as age and size on TNFR:Fc pharmacokinetics *in children with juvenile rheumatoid arthritis.*

Data Analysis and Results:

The analysis was done in three stages; base model development, full model development, and model reduction. In addition the data was included gradually to identify potential problems. Both strategies are acceptable. The pharmacokinetic parameters for the final model are presented in table 1 below.

TABLE 1.

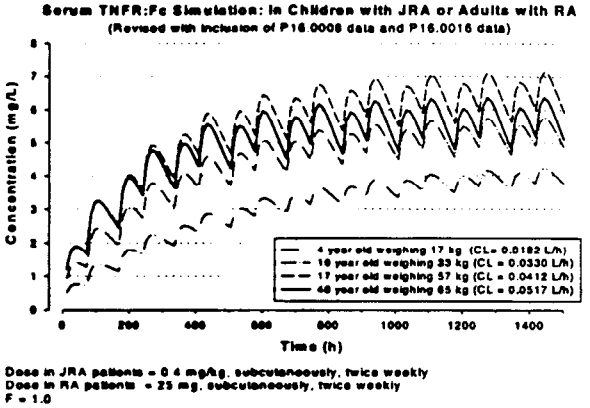
TABLE 3. REDUCTION OF POPULATION PHARMACOKINETIC MODEL

Description (CV [a])	θ_1 [b]	θ_2 [c]	θ_3 [d]	θ_4 [e]	θ_5 [f]	θ_6 [g]	θ_7 [h]	θ_8 [h]	θ_9 [h]	θ_{10} [h]	Objective Function (Δ OF)
FULL model [i] OF = 37061.9	0.123 (8.7%)	4.74 (28%)	0.061 (14%)	3.47 (6.7%)	0.051 (7.4%)	0.703 (5.7%)	9.30 (35%)	7E-11 (4E7%)	0.064 (14%)	0.057 (34%)	0.0 [o]
FULL model with AGE on CL removed [j] OF = 37073.0	0.037 (18%)	1.87 (49%)	0.0044 (16%)	1.94 (14%)	0.045 (9.2%)	0.726 (6.6%)	6.5E-4 (12%)	0.024 (15%)	0.090 (16%)	-	↑ 11.1 (sig.) [p]
FULL model with WGT on CL removed [k]	0.123 (7.8%)	4.72 (28%)	0.061 (14%)	3.47 (6.8%)	0.051 (7.5%)	0.705 (5.7%)	9.28 (34%)	0.064 (13%)	0.058 (33%)	-	no Δ (not sig.) [o]
FULL model with WGT on CL removed, RA on CL removed [l]	0.102 (6.0%)	3.83 (24%)	0.0054 (13%)	2.33 (13%)	0.044 (8.6%)	0.754 (5.8%)	9.16 (17%)	0.059 (24%)	-	-	↑ 147.7 (sig.) [p]
FULL model with WGT on CL removed, WGT on V removed [m]	0.105 (6.0%)	8.43 (< 1%)	0.0052 (15%)	2.20 (16%)	0.046 (9.0%)	0.730 (5.9%)	7.35 (20%)	0.081 (8.8%)	-	-	↑ 12.7 (sig.) [p]
FINAL MODEL with AGE on CL; RA status on CL; WGT on V [n]; OF=37061.9	0.123 (7.8%)	4.72 (28%)	0.061 (14%)	3.47 (6.8%)	0.051 (7.5%)	0.703 (5.7%)	9.28 (34%)	0.064 (13%)	0.058 (33%)	-	0.0

a. Precision of the parameter estimate by the model expressed as a coefficient of variation. (= se/θ)
b. Parameter describing clearance
c. Parameter describing volume of distribution
d. Parameter describing intercompartmental clearance
e. Parameter describing additive term for VSS where VSS=θ_3 + θ_4
f. Parameter describing the first-order absorption rate constant
g. Bioavailability of TNFR:Fc after SC dose, relative to IV dose
h. Respective covariate parameter
i. θ_1 = $CLMAX_{0,wt}$ in patients without RA, (L/hr); θ_6 = AGE50 (yr); θ_7 = weight factor on clearance; θ_8 = $CLMAX_{0,wt}$ in patients with RA, (L/hr); θ_{10} = weight factor on volume
j. θ_1 = $CLMAX_{0,wt}$ (L/hr); θ_7 = weight factor on clearance; θ_8 = $CLMAX_{0,wt}$ in patients with RA, (L/hr); θ_9 = weight factor on volume
k. θ_1 = $CLMAX_{0,wt}$ (L/hr); θ_6 = AGE50 (yr); θ_7 = $CLMAX_{0,wt}$ (L/hr); θ_8 = weight factor on volume
l. θ_1 = CLMAX (L/hr); θ_6 = AGE50 (yr); θ_7 = weight factor on clearance
m. θ_1 = $CLMAX_{0,wt}$ (L/hr); θ_6 = AGE50 (yr); θ_7 = $CLMAX_{0,wt}$ (L/hr)
n. Significance during this step assessed with a 7.9 point decrease in OF (p<0.05, assuming a chi-square distribution)
o. Change in OF = relative to FULL model
p. Change in OF = relative to FULL model with AGE on CL removed

The final estimates of the population pharmacokinetic parameters were then used to simulate concentration-time profiles for children of various ages as well as an adult with rheumatoid arthritis (Figure 1).

FIGURE 1



Reviewers Comment:

1. *The model building and development strategies are well-planned and standard procedure for this type of analysis. There are, however, a few steps in the analysis that can be criticized such as:*
   a. *The data that is used needs further cleanup. For example there are zero concentrations included that will adversely affect the fit of the model to the data. Many of the zero values were eliminated by the sponsor by commenting out the row in the data set (indicated by a "c" at the start of line), apparently because of large weighted residuals for these points, however, a number of such data points were still included (see table 2 and 3). Zero values at the end of the concentration time curve are particularly influential and should be excluded. For example patient ——— has values of zero on day 20 from 216 hrs to 480 hrs.*

TABLE 2

ID	DATE	TIME	DOSE	RATE	CMT	SS	II	PREP	EVID	CP
	1	168	.	.	.	.	.	1	0	.
	1	272	.	.	.	.	.	1	0	.
	28	216	.	.	.	.	.	0	0	.
	28	240	.	.	.	.	.	0	0	.
	28	144	.	.	.	.	.	0	0	.
	29	480	.	.	.	.	.	1	.	.
	29	384	.	.	.	.	.	1	.	.
	29	36	.	.	.	.	.	1	.	.
	29	480	.	.	.	.	.	1	.	.
	29	480	.	.	.	.	.	1	.	.
	1	120	.	.	.	.	.	1	.	.
	29	216	.	.	.	.	.	1	.	.
	29	264	.	.	.	.	.	1	.	.
	29	312	.	.	.	.	.	1	.	.
	29	384	.	.	.	.	.	1	.	.
	29	480	.	.	.	.	.	1	.	.
	1	12	.	.	.	.	.	0	0	.
	1	168	.	.	.	.	.	0	0	.
	1	336	.	.	.	.	.	0	0	.
	1	672	.	.	.	.	.	0	0	.
	1	672	.	.	.	.	.	0	0	.
	1	672	.	.	.	.	.	0	0	.
	14	23 42	.	.	.	.	.	1	0	.
	119	22 7	.	.	.	.	.	1	0	.
	106	22 17	.	.	.	.	.	1	0	.
	121	23 5	.	.	.	.	.	1	0	.
	88	1 42	.	.	.	.	.	1	0	.
	116	0 17	.	.	.	.	.	1	0	.
	120	23	.	.	.	.	.	1	0	.
	90	23	.	.	.	.	.	1	0	.
	124	2 33	.	.	.	.	.	1	0	.
	119	22 5	.	.	.	.	.	1	0	.
	88	0	.	.	.	.	.	1	0	.
	29	0 75	.	.	.	.	.	1	0	.
	29	23 33	.	.	.	.	.	1	0	.
	106	0 42	.	.	.	.	.	1	0	.
	98	0.5	.	.	.	.	.	1	0	.
	104	0	.	.	.	.	.	1	0	.
	106	23 15	.	.	.	.	.	1	0	.
	108	22 35	.	.	.	.	.	1	0	.
	120	2 67	.	.	.	.	.	1	0	.
	136	19 88	.	.	.	.	.	1	0	.

TABLE 3

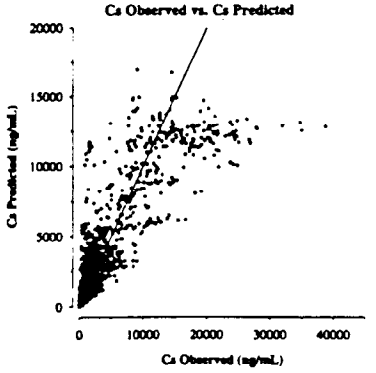
ID	DATE	TIME	DOSE	RATE	CMT	SS	II	PREP	EVID	CP
	1	0	.	.	.	.	.	1	0	0
	1	0	.	.	.	.	.	1	0	0
	1	0	.	.	.	.	.	1	0	0
	1	0	.	.	.	.	.	1	0	0
	1	0	.	.	.	.	.	1	0	0
	1	0 083	.	.	.	.	.	0	0	0
	1	0.25	.	.	.	.	.	0	0	0
	1	0 5	.	.	.	.	.	0	0	0
	1	0 083	.	.	.	.	.	0	0	0
	1	0.25	.	.	.	.	.	0	0	0
	1	0.5	.	.	.	.	.	0	0	0
	1	0 083	.	.	.	.	.	0	0	0
	1	0.25	.	.	.	.	.	0	0	0
	1	0.5	.	.	.	.	.	0	0	0
	1	0.5	.	.	.	.	.	0	0	0
	1	0 083	.	.	.	.	.	0	0	0
	1	0 083	.	.	.	.	.	0	0	0
	1	0.25	.	.	.	.	.	0	0	0
	1	1	.	.	.	.	.	0	0	0
	1	2	.	.	.	.	.	0	0	0

b. *The structural model appears to require the inclusion of a lag time for absorption of the drug from the subcutaneous injection site, which the sponsor did not consider.. Using the full data set as well as an abridged version (minus 24 zero data points) inclusion of a lag time reduces the objective function by 179 which is statistically significant ($p<0.0005$).*

c. *The structural model appears to be deficient in that the peak concentrations are not well predicted. This is manifested in the truncated appearance of the plot of the predicted versus observed concentrations at around 1500 ng/ml (see figure 2). It appears that the main reason for this truncation is that the maximum concentrations (Cmax) after iv administration are not well predicted. This could be due to an incorrect pharmacokinetic structural model. Of particular interest is the fact that all infusions are fixed in the data file as being given over 30 minutes whereas peak concentrations are observed well beyond this time (up to 2 hours) in many of the subjects. This could be due to incorrect recording of the infusion time or some other factor such as distribution anomalies.*

FIGURE 2

TNFR:Fc OBSERVED VS. PREDICTED CONCENTRATIONS OR TIME FROM NM_626 FINAL POPULATION PHARMACOKINETIC MODEL
(Revised with inclusion of P16.0008 and P16.0016 data)



2. *Re-analysis of the data by this reviewer after removal of the zero values produced slightly different results that appear to be more realistic (See final model in Table 4). Predicted versus observed plots of the final model are presented in figures 3 and 4 as an indication of goodness of fit.*

a. *Inclusion of a lag time in the two compartment structural model decreased the objective function by 179 units which is statistically significant ($p<0.0005$).*

b. *In building the covariate model the main difference to the sponsor's results was that weight was found to be a significant covariate. The decrease in objective function with its removal was 133 which is statistically significant ($p<0.005$). In addition the breakpoint in age for the influence of age on clearance plateau's sooner, 1.27 years as calculated by the reviewers model compared to 9.28 years calculated by the sponsor.*

Table 4. POPULATION PHARMACOKINETIC MODEL

Description	θ_1 cl	θ_2 v2	θ_3 Q	θ_4 v3	θ_5 ka	θ_6 f	θ_7 lag	θ_8 RA	θ_9 sl-cl	θ_{10} sl-v	θ_{11} age	ΔOBF (OBF)
Base Model OBF=37250	0.0942	8.4	0.00616	2.68	0.0355	1.1						0
Base Model + lag time	0.107	7.19	0.0451	3.74	0.0275	1.4	0.0375					↓179 (37071)
Base Model + lag time + RA	0.109	7.93	0.0678	3.18	0.0388	0.961	0.501	0.447				↓ 559 (36512)
Base Model + weight on Cl + RA + lag time	0.0324	1.94	0.0744	2.75	0.0458	0.771	0.47	0.273	0.00087	0.0803		↓64 (36448)
Base Model + age on Cl + RA + lag time	0.127	4.12	0.0579	3.23	0.041	0.928	0.445	0.314		0.0476	6.93	↓148 (36364)
Base Model + age & weight on Cl + RA + lag time	0.0407 (39%)	2.53 (59%)	0.0685 (18%)	3.22 (8%)	0.04 (10%)	0.945 (8%)	0.456 (7%)	0.205 (29%)	0.0009 (18%)	0.0687 (30%)	1.27 (116%)	↓133 (36231)
Sponsor Model	0.12 (7%)	4.97 (26%)	0.063 (15%)	3.46 (7%)	0.0516 (7%)	0.703 (6%)	–	0.0603 (13%)	–	0.0547 (35%)	8.0 (36%)	(36828)

FIGURE 3

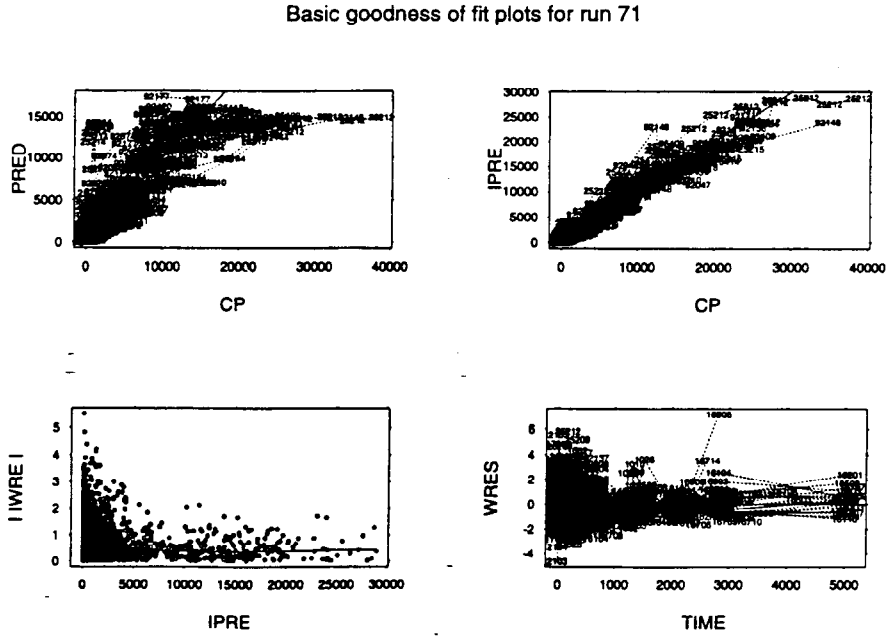
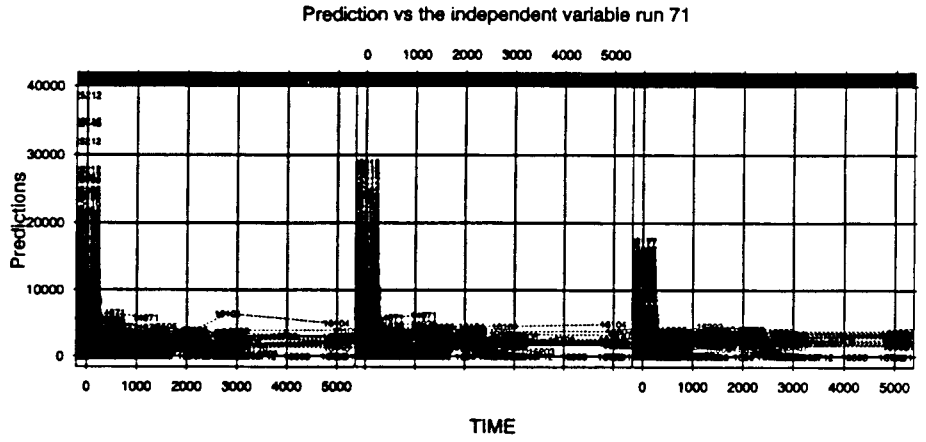


FIGURE 4



3. *The significance of these results are the following:*
   a. *The current model predicts the observed concentrations better than the model generated by the sponsor. From figure 1 it is clear that using the sponsors model for a four year old 17 kg patient an average steady-state concentration (Css) of between 3 and 4 ug/ml is predicted, whereas, the reviewers model predicts a Css of around 2.4. This latter value is closer to the naïve average concentration of the observed value in these patients of 2.1 ug/ml. In addition, the sponsors model predicts that for a 40 year old 65 kg person steady state concentrations achieved with a dose of 25 mg twice a week vary between about 5 and 6.5 ug/ml. Observed median concentrations in RA patients was 3 ug/ml (range 1.7 to 5.6 ug/ml) which is closer to the prediction of 3.9 ug/ml made with the reviewer model.*

Fig 5. Plot of Concentration versus Age

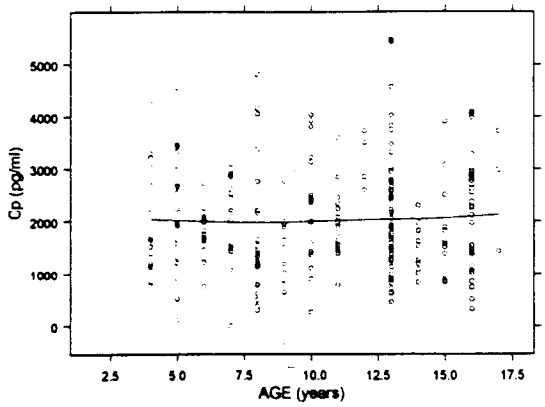
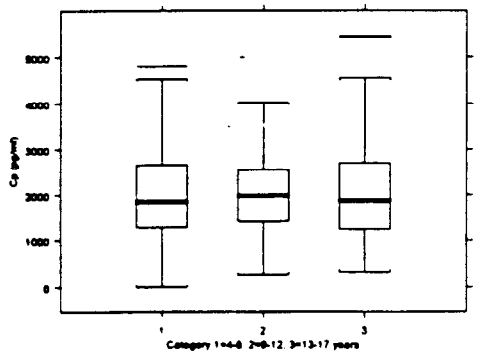
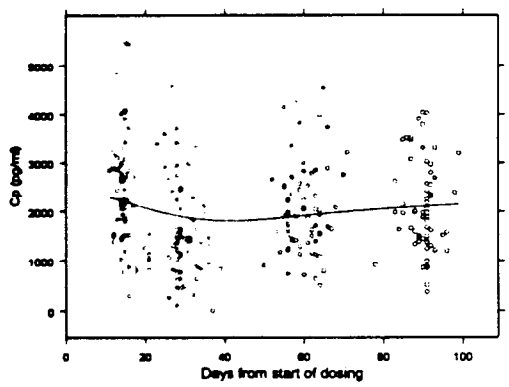


Figure 6 Plasma Concentration versus age category



2. Are serum concentrations at steady state?
In adults the half-life of enbrel was estimated at about 3 days. With continuous dosing steady state should be achieved by 15 days. In children the half-life appears to be slightly longer (about 4 days), however by day 20 should be at steady state. A scatterplot with a spline smooth of plasma concentration versus number of days after initiating enbrel dosing indicates relatively constant concentrations from day 20 to day 100 (Figure 7). It appears, therefore, that it is likely that plasma concentrations of enbrel are at steady state.

Figure 7 Plot of Concentration versus time in days



3. Would changing disease activity influence drug exposure?
   The sponsor determined a 50% lower clearance in patients with RA and JRA than other subjects. The reviewer calculated a 20% lower clearance in these patients. This is simply a reflection of the difference between healthy subjects and patients with RA and JRA.

4. Would displacement of NSAID's from protein binding by Enbrel be responsible for any drug-drug interaction?
   This is unlikely since NSAID's generally are low extraction ratio drugs. Any displacement of NSAID from protein binding would cause an increase in total clearance of drug but not unbound drug. The result would be a decreased total concentration and an unchanged free concentration. The activity would be unlikely to change. Acute changes in binding are also unlikely since Enbrel (the displacer) is slowly absorbed after sc administration and accumulates over a period of three to four weeks thus allowing equilibration of bound and free NSAID to take place over a period of time.

R. Miller 5/14/99

Raymond Miller, D.Sc.

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